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Cost-Effectiveness of the 21-Gene Assay for Guiding Adjuvant Chemotherapy Decisions in Early Breast Cancer

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ABSTRACT

Objectives: Adjuvant chemotherapy decisions in early breast cancer are complex. The 21-gene assay can potentially aid such decisions, but costs US $4175 per patient. Adjuvant! Online is a freely available decision aid. We evaluate the cost-effectiveness of using the 21-gene assay in conjunction with Adjuvant! Online, and of providing adjuvant chemotherapy conditional upon risk classification. **Methods:** A probabilistic Markov decision model simulated risk classification, treatment, and the natural history of breast cancer in a hypothetical cohort of 50-year-old women with lymph node–negative, estrogen receptor– and/or progesterone receptor–positive, human epidermal growth factor receptor 2/neu–negative early breast cancer. Cost-effectiveness was considered from an Ontario public-payer perspective by deriving the lifetime incremental cost (2012 Canadian dollars) per quality-adjusted life-year (QALY) for each strategy, and the probability each strategy is cost-effective, assuming a willingness-to-pay of $50,000 per QALY. **Results:** The 21-gene assay has an incremental cost per QALY in patients at low, intermediate, or high Adjuvant Online! risk of $22,440 (probability cost-effective 78.46%), $2,526 (99.40%), or $1,111 (99.82%), respectively. In patients at low (high) 21-gene assay risk, adjuvant chemotherapy increases (reduces) costs and worsens (improves) health outcomes. For patients at intermediate 21-gene assay risk and low, intermediate, or high Adjuvant! Online risk, chemotherapy has an incremental cost per QALY of $44,088 (50.59%), $1,776 (77.65%), or $1,778 (82.31%), respectively. **Conclusions:** The 21-gene assay appears cost-effective, regardless of Adjuvant! Online risk. Adjuvant chemotherapy appears cost-effective for patients at intermediate or high 21-gene assay risk, although this finding is uncertain in patients at intermediate 21-gene assay and low Adjuvant! Online risk.

Keywords: breast cancer, chemotherapy, cost-effectiveness analysis, decision making, pharmacogenetics.

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Introduction

Adjuvant chemotherapy decisions for women with early stage breast cancer are complex. At present, decisions are informed by clinical judgment, often supplemented through the use of Adjuvant! Online [1]. Adjuvant! Online is a free online diagnostic tool that estimates a woman's risk of breast cancer–specific mortality (BCSM) or relapse on the basis of information entered by the physician, including the woman's age, comorbidities, tumor size, estrogen receptor status, number of involved lymph nodes, and proposed course of treatment [2]. Results can be categorized as "low" (BCSM $< 9\%$), "intermediate" ($9\% \leq$ BCSM $< 17\%$), or "high" (BCSM $\geq 17\%$) risk [3]. A validation study of Adjuvant! Online has found a high degree of correlation between predicted and observed survival [4].

An alternative predictive tool has recently become available. The 21-gene assay (Oncotype DX, Genomic Health, Redwood City, CA) quantifies the expression of 21 genes in breast cancer tissue by performing reverse transcription polymerase chain reaction on formalin-fixed paraffin-embedded tumor blocks that are obtained during initial surgery. Results are summarized by a "Recurrence Score" (RS) between 0 and 100, with scores categorized as "low" ($RS < 18$), "intermediate" ($18 \leq RS < 30$), or "high" ($RS \geq 30$) risk [5]. It has been validated both in women with estrogen receptor–positive early stage breast cancer that is lymph node–negative, and in women with estrogen receptor–positive breast cancer that is lymph node–positive, as a means to predict the risk of distant recurrence and magnitude of chemotherapy benefit when added to endocrine therapy [6–9].

As of April 2012, the 21-gene assay cost US $4175 per patient [10]. Its cost-effectiveness is therefore a matter of considerable policy interest. There is also uncertainty as to the clinical- and cost-effectiveness of providing adjuvant chemotherapy, particularly to patients at intermediate risk [11,12]. We present a cost-effectiveness analysis that comprehensively addresses both these issues. An earlier version of our analysis formed part of a

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recent review of gene expression profiling tests carried out by the Ontario Ministry of Health and Long-Term Care [13].

Methods

Overview

We conducted a cost-effectiveness analysis from the perspective of the Ontario Ministry of Health and Long-Term Care. The analysis had two objectives:

1. To evaluate the outcomes, costs, effectiveness, and cost-effectiveness of the 21-gene assay, when used in conjunction with Adjuvant! Online.
2. To evaluate the outcomes, costs, effectiveness, and cost-effectiveness of providing adjuvant chemotherapy, conditional upon a patient's predicted risk of distant recurrence.

The patient population was a hypothetical cohort of 50-year-old women diagnosed with lymph node–negative, estrogen receptor– and/or progesterone receptor– positive, human epidermal growth factor receptor 2 (HER2/neu)–negative early breast cancer, who are candidates for adjuvant chemotherapy. The cohort was followed over a lifetime. Costs were measured in 2012 Canadian dollars, and a discount rate of 5% was applied to costs and outcomes [14]. The analysis was conducted in April 2012.

We conducted our analysis in consultation with an expert panel convened by the Ontario Ministry of Health and Long-Term Care [15]. The expert panel provided input on the appropriate model structure and parameters.

Model

The model is described in Figure 1. The structure was informed by an existing model by Tsoi et al. [16]. Patients were first stratified by Adjuvant! Online risk group. Each Adjuvant! Online risk group might then be provided with the 21-gene assay; if provided, the respective Adjuvant! Online risk group was further stratified by 21-gene assay risk group. This resulted in patients being assigned to 1 of 12 risk categories (see Fig. 1 legend). All patients were then assumed to undertake adjuvant tamoxifen treatment for 5 years, with some patients also receiving adjuvant chemotherapy. Higher risk patients were assumed to receive more complex chemotherapy regimens, as detailed below. All chemotherapy patients risked toxicity requiring hospital treatment. Patients were initially assumed to be distant recurrence free, but risked developing a distant recurrence over their lifetime. All patients eventually died, either because of breast cancer or for other reasons. The model was developed by using TreeAge Pro 2009 (TreeAge Software, Inc., Williamstown, MA), Microsoft Excel 2010 (Microsoft, Seattle, WA), and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

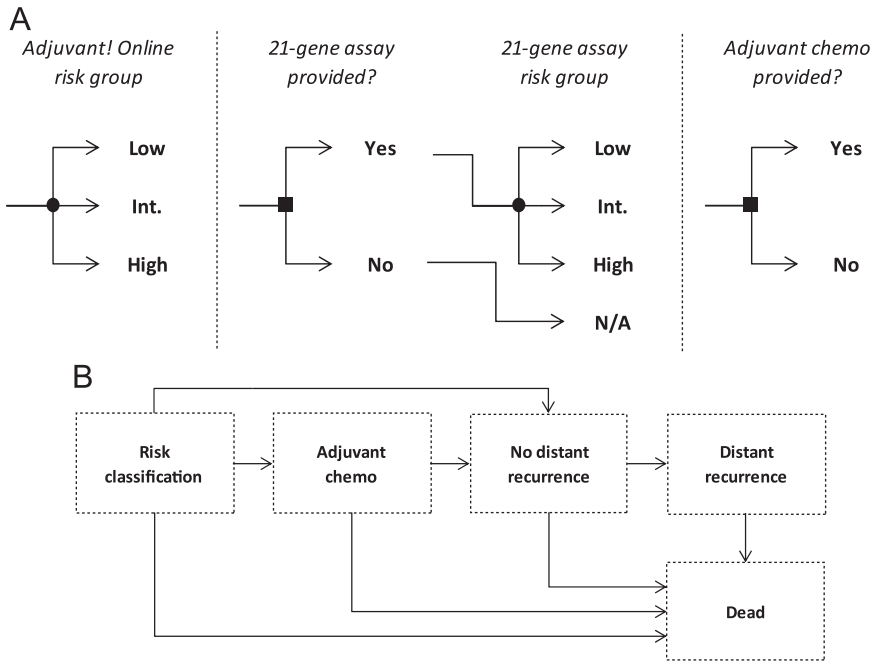

Fig. 1 – Model schematic. (A) Decision tree representing the risk classification process and adjuvant chemotherapy decision. Decision nodes are represented by squares, while chance nodes are represented by circles. The decision about whether to provide the 21-gene assay is made independently for each Adjuvant! Online risk group. The 21-gene assay stratifies patients into three possible risk groups when provided ("low," "int.," and "high") or one possible risk group when not provided ("N/A"). Because patients in the N/A risk group face a different risk of distant recurrence to patients in any of the low-, int.-, and high-risk groups, the model considers four unique risk groups resulting from the decision to provide or not provide the 21-gene assay. Because patients in any one of the three Adjuvant! Online risk groups may be assigned to any one of the four 21-gene assay risk groups, the model assigns each patient to 1 of 12 (3 × 4) unique risk "categories." Each risk category represents a unique combination of the Adjuvant! Online and 21-gene assay risk groups. The adjuvant chemotherapy decision is considered independently for each of the 12 risk categories resulting from risk classification. (B) Markov model representing patients' progression through risk classification and the possible provision of adjuvant chemotherapy, possible distant recurrence, and death. Int., intermediate; N/A, not available.

Parameters

The model parameters are summarized in Table 1.

Probabilities

Proportion of patients assigned to each risk category. The proportion of patients assigned to each of the 12 risk categories was estimated from Bryant's retrospective analysis of Adjuvant! Online and the 21-gene assay as predictors of 10-year distant recurrence by using data and samples gathered from a subset of 668 patients enrolled in the tamoxifen arm of the NSABP B-14 study (see Appendix A in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.03.1625) [3,6].

Proportion of patients in each risk category provided adjuvant chemotherapy. A number of studies have attempted to measure the impact of the 21-gene assay on adjuvant clinical decision making [17,32–35]. The study by Lo et al. [17] is the only prospective study in a North American population that reports the proportion of patients assigned to receive chemotherapy before and after the 21-gene assay results are known, stratified by 21-gene assay risk group. Because the authors did not report the proportion of patients assigned to receive chemotherapy for each of the 12 risk categories in our model, we estimated the proportion for each risk category by using linear regression to derive a relationship between the baseline risk of distant recurrence and the proportion of patients assigned to receive chemotherapy. Because knowledge of the 21-gene assay results has the potential to change clinician behavior, separate relationships were estimated for before and after the results are known (see Appendix B in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.03.1625).

Choice of Treatment. All patients were assumed to be provided 20 mg tamoxifen treatment daily for 5 years. Some patients were also assumed to be provided adjuvant chemotherapy, with a greater proportion of patients assumed to receive adjuvant chemotherapy in risk categories at higher baseline risk of distant recurrence. Following advice from the expert panel, higher risk patients were assumed to receive more complex chemotherapy regimens.

Patients in the 21-gene assay low-risk group provided with adjuvant chemotherapy were assumed to receive CMF chemotherapy: oral cyclophosphamide 100 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2, given 4-weekly for six cycles.

Adjuvant chemotherapy patients in the 21-gene assay intermediate risk group were assumed to receive TC chemotherapy: docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2, given 3-weekly for four cycles. The Ontario Ministry of Health and Long-Term Care funds secondary prophylactic granulocyte colony-stimulating factor (G-CSF) prophylaxis with filgrastim for some low-income patients and those older than 65 years (assumed to account for 40% of all patients). It was assumed that 33% of TC chemotherapy patients would require secondary G-CSF prophylaxis [36].

Adjuvant chemotherapy patients in the 21-gene assay high-risk group were assumed to receive FEC-D chemotherapy: 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 (FEC), given 3-weekly for three cycles, followed by docetaxel 100 mg/m^2 given 3-weekly for three cycles. For FEC-D chemotherapy, the Ontario Ministry of Health and Long-Term Care funds primary G-CSF prophylaxis with filgrastim alongside docetaxel and secondary G-CSF prophylaxis alongside FEC and docetaxel. It was assumed that patients funded by the Ministry (40% of all patients) would receive primary G-CSF prophylaxis alongside docetaxel and that 15% of these patients would receive secondary G-CSF prophylaxis alongside FEC or docetaxel.

G-CSF prophylaxis was assumed to consist of 300 mcg filgrastim per day for 10 days, provided alongside half of chemotherapy cycles [37].

For adjuvant chemotherapy patients not provided with the 21-gene assay, the choice of chemotherapy regimen was assumed to be determined in a similar manner by the Adjuvant! Online risk group.

Risk of Hospital Visit Due to Chemotherapy Toxicity. A proportion of patients undergoing chemotherapy was assumed to require a hospital admission due to toxicity. Recent data on the proportion of breast cancer patients visiting the hospital within 4 weeks of any cycle of adjuvant chemotherapy were obtained from the Canadian Institute for Health Information [18].

Risk of Distant Recurrence. There are no published prospective studies reporting distant recurrence conditional upon 21-gene assay or Adjuvant! Online risk. The retrospective analysis by Bryant [3] using data from a subset of 668 patients enrolled in the tamoxifen arm of the NSABP B-14 study reported estimates of the risk of distant recurrence without adjuvant chemotherapy for some (but not all) of the risk categories in our model. A further retrospective analysis by Paik et al. [7] provided estimates of the risk of distant recurrence with and without CMF chemotherapy, using data and samples gathered from a subset of 651 patients enrolled in the NSABP B-20 study. These results were stratified by 21-gene assay risk group only.

We used the findings from Bryant and Paik et al. to derive the 10-year risk of distant recurrence without adjuvant chemotherapy for each risk category. The distant recurrence-free survival curves reported by Bryant revealed considerable overlap between the intermediate and high Adjuvant! Online risk groups. Therefore, a common risk of distant recurrence was assumed for both risk groups. In reporting estimates of the risk of distant recurrence, Bryant merged the intermediate and high 21-gene assay risk groups. We imputed separate estimates for each by using a calibration model developed in WinBUGS (see Appendix C in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.03.1625).

The Ontario-based expert panel, however, expressed concern that the average risk of 10-year distant recurrence of 14.8% observed in the subset of the NSABP B-14 study analyzed by Bryant was likely to be higher than that in the current Ontario target population. The lower average risk of 11.4% observed in the subset of the NSABP B-20 study analyzed by Paik was regarded as more appropriate for Ontario. We therefore applied a proportional adjustment to the estimate for each risk category so that the aggregate risk of distant recurrence across each 21-gene assay risk group was commensurate with the estimates reported by Paik et al. from the NSABP B-20 study.

Next, we derived estimates of the relative risk of 10-year distant recurrence with CMF chemotherapy for each risk category. Because the relative risk estimates reported by Paik et al. were stratified by 21-gene assay risk group only, we developed a regression model by using WinBUGS and Microsoft Excel to impute the relative risk for each risk category (see Appendix C in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.03.1625).

Estimates of the 10-year risk of distant recurrence with more complex chemotherapy regimens were derived by estimating the relative risk of distant recurrence for TC versus CMF and for FEC-D versus CMF from the results of published trials (see Appendix C

Table 1 – Model parameters.

Parameter (Distribution*) [Source]	Value
Probabilities	
Proportion of patients assigned to each risk category (%) (Dirichlet) [3]	
Adjuvant! Online low risk	
21-gene assay low risk	32.34
21-gene assay intermediate risk	12.57
21-gene assay high risk	8.08
Total for Adjuvant! Online low risk	52.99
Adjuvant! Online intermediate risk	
21-gene assay low risk	8.53
21-gene assay intermediate risk	3.59
21-gene assay high risk	6.59
Total for Adjuvant! Online intermediate risk	18.71
Adjuvant! Online high risk	
21-gene assay low risk	9.73
21-gene assay intermediate risk	6.14
21-gene assay high risk	12.43
Total for Adjuvant! Online high risk	28.29
Proportion of patients in each risk category provided adjuvant chemotherapy (%) (Beta) [17]	
Adjuvant! Online low risk	
21-gene assay low risk	9.79
21-gene assay intermediate risk	17.62
21-gene assay high risk	63.44
21-gene assay not provided	46.05
Adjuvant! Online intermediate risk	
21-gene assay low risk	13.73
21-gene assay intermediate risk	36.56
21-gene assay high risk	98.61
21-gene assay not provided	55.06
Adjuvant! Online high risk	
21-gene assay low risk	13.72
21-gene assay intermediate risk	36.65
21-gene assay high risk	99.73
21-gene assay not provided	57.57
Risk of hospital visit due to toxicity (%) (Beta) [18]	17.04
Cause of hospital visits due to toxicity (%) (Dirichlet) [18]	
Neutropenia/fever/infections	53.56
Injuries & trauma	11.48
Malignant neoplasm	10.89
Pain & pain management	7.51
Nausea/vomiting/dehydration	6.02
Gastrointestinal tract	5.64
Chest pain	4.89
Risk of 10 year distant recurrence without chemotherapy (%) (Beta) [3,7]	
Adjuvant! Online low risk	
21-gene assay low risk	2.61
21-gene assay intermediate risk	5.78
21-gene assay high risk	24.78
21-gene assay not provided	6.75
Adjuvant! Online intermediate risk	
21-gene assay low risk	4.24
21-gene assay intermediate risk	13.40
21-gene assay high risk	45.71
21-gene assay not provided	20.60
Adjuvant! Online high risk	
21-gene assay low risk	4.24
21-gene assay intermediate risk	13.40
21-gene assay high risk	45.71
21-gene assay not provided	24.12
Risk of 10 year distant recurrence with chemotherapy (%) (Beta) [3,7,19–23]	
Adjuvant! Online low risk	
21-gene assay low risk	3.81
21-gene assay intermediate risk	4.46
21-gene assay high risk	6.48
21-gene assay not provided	4.93
Adjuvant! Online intermediate risk	
21-gene assay low risk	4.64
21-gene assay intermediate risk	6.23
21-gene assay high risk	7.37
21-gene assay not provided	6.07
Adjuvant! Online high risk	
21-gene assay low risk	5.79
21-gene assay intermediate risk	8.18
21-gene assay high risk	8.91
21-gene assay not provided	7.68
Risk of mortality due to toxicity (%) (Beta) [24]	0.35
Median life expectancy following distant recurrence (mo) (Normal) [25]	21.0
Risk of mortality due to other causes (Fixed) [26]	Life table
Costs (2012 Canadian dollars)	
Cost of 21-gene assay (per patient) ($) (Fixed) [10,27]	
21-gene assay (2012 US dollars)	4175.00
US/Canadian dollar exchange rate (30 April 2012)	0.9879
21-gene assay (2012 Canadian dollars)	4124.48
Chemotherapy costs applicable to all regimens (per cycle) ($) (Fixed) [16]	
Laboratory tests	62.06
Human resources	147.52
CMF specific costs (per cycle) ($) (Fixed)‡	
Cyclophosphamide 600 mg/m^2	2.26
Methotrexate 40 mg/m^2	3.22
5-fluorouracil 600 mg/m^2	8.22
TC specific costs (per cycle) ($) (Fixed)‡	
Docetaxel 75 mg/m^2	534.14
Cyclophosphamide 600 mg/m^2	39.06
FEC-D specific costs (per cycle) ($) (Fixed)‡	
5-fluorouracil 500 mg/m^2	6.65
Epirubicin 100 mg/m^2	80.72
Cyclophosphamide 500 mg/m^2	33.23
Docetaxel 100 mg/m^2 = 173mg	712.19
G-CSF prophylaxis (per day) ($) (Fixed)‡	
Filgrastim 300 mcg	184.36
Hormone therapy (per day) ($) (Fixed)‡	
Tamoxifen 20 mg	0.11
Ongoing care for recurrence-free patients (per month) ($) (Fixed) [28]	
1st Year	55.24
2nd Year	49.89
3rd Year	44.54
4th Year	39.19
5th Year and beyond	3.83
Cost of treating distant recurrence ($) (Modeled†*)* [28]	
Initial cost of treatment (one time)	8,356.23
Ongoing care (per month)	717.57
End of life care (last 3 months) ($) (Modeled†*)* [28]	22,040.96
Treatment of non-fatal chemotherapy toxicity ($) (Log normal) [29]	
Neutropenia/fever/infections	6,827.45
Injuries & trauma	8,730.53
Malignant neoplasm	6,754.79

Table 1 – *continued*

Parameter (Distribution*) [Source]	Value
Pain & pain management	4,352.07
Nausea/vomiting/dehydration	4,142.12
Gastrointestinal tract	6,773.66
Chest pain	3,022.78
Treatment of fatal toxicity ($) (Log normal) [29]	33,807.98
Utility weights	
First year following diagnosis (while on hormone therapy) *(Beta)* [30]	0.744
First year following diagnosis (while on chemotherapy) *(Beta)* [30]	0.620
Second and following years prior to distant recurrence *(Beta)* [30]	0.779
Following distant recurrence *(Beta)* [30]	0.685
Dead *(Fixed)* [30]	0

*Distributions were assigned to parameters according to conventional practice in economic evaluations, as described in the textbook by Briggs et al. [31]. Probabilities and proportions were assigned beta distributions (in the case of events with two outcomes) or Dirichlet distributions (in the case of events with three or more outcomes). In either case the parameters of the distribution were informed by the frequency of each outcome observed in the relevant study. Median life expectancy was assigned a normal distribution due to the approximately symmetrical distribution reported by Chang et al. [25]. The costs associated with treatment of chemotherapy toxicity were assigned lognormal distributions since the cost data were highly skewed and positive. Utility weights were assigned beta distributions to constrain the possible values between 0 and 1, with the exception of the utility weight for the 'dead' state which was fixed at 0. Where no measure of uncertainty was available, a fixed value was used. Further details on the distributions assigned to parameters are available from the authors on request.

† The costs for treating distant recurrence were estimated by modeling the treatment pathway described in Figure 4 of the study by Will et al. [28]. To account for parameter uncertainty, probabilities were assigned beta distributions according to the number of events at each node implied by the study sample size.

‡ Princess Margaret Cancer Centre Inpatient and Outpatient Pharmacy (personal communication, Feb 29, 2012)

in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.03.1625) [19–23].

Risk of Mortality. The risk of death from causes other than breast cancer was taken from relevant life tables [26]. Patients were subject to a higher risk of mortality during chemotherapy and following distant recurrence [24,25].

Costs

All costs were inflated to 2012 Canadian dollars by using the Ontario health care inflation index [38].

21-Gene assay. The manufacturer's list price for the 21-gene assay was converted to Canadian dollars by using the closing exchange rate on April 30, 2012 [10,27].

Adjuvant tamoxifen and chemotherapy. The costs associated with providing adjuvant tamoxifen and chemotherapy were obtained from the Princess Margaret Cancer Centre Inpatient and Outpatient Pharmacy (personal communication, February 29, 2012).

Hospital visit due to chemotherapy toxicity. The costs associated with hospital visits resulting from chemotherapy toxicity were estimated from acute inpatient costs collected by the Ontario Case Costing Initiative [29].

Ongoing care, distance recurrence, and terminal care. The average costs associated with ongoing care prior to distant recurrence, treatment of distant recurrence, and ongoing and terminal care following distant recurrence were derived from a comprehensive study of the lifetime costs of breast cancer treatment in Canada [28].

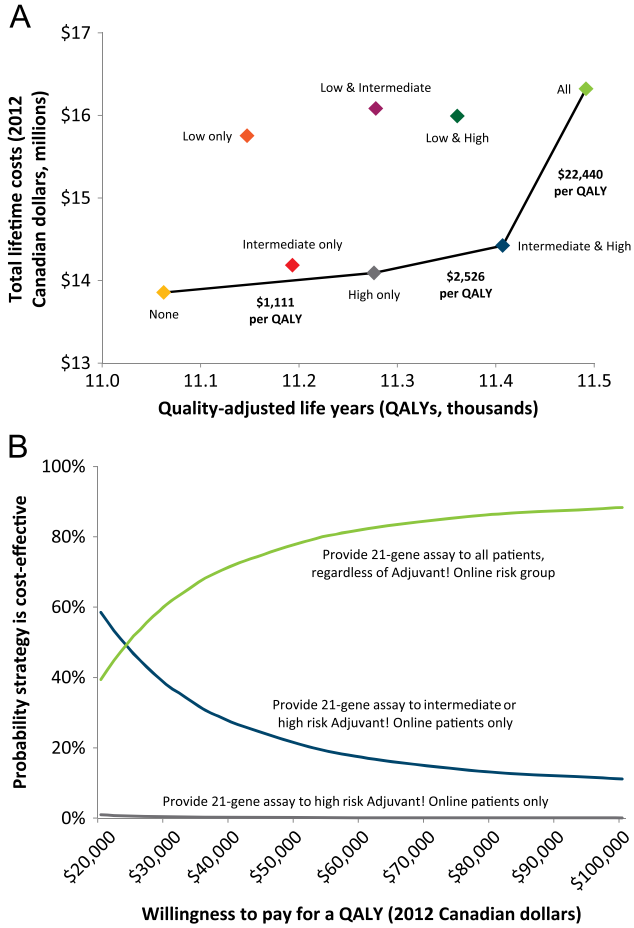

Fig. 2 – Cost-effectiveness of providing the 21-gene assay. (A) Total lifetime costs and QALYs of each strategy for the provision of the 21-gene assay across Adjuvant! Online risk groups. Label names refer to the Adjuvant! Online risk groups provided with the 21-gene assay under each strategy. The black line represents the efficiency frontier. The slope of the efficiency frontier between pairs of strategies represents the incremental cost-effectiveness ratio (ICER) of the more expensive strategy versus the less expensive strategy. (B) Probability that each strategy for the provision of the 21-gene assay across Adjuvant! Online risk groups is cost-effective, conditional upon willingness to pay for a QALY. Strategies not represented have less than 1% probability of being cost-effective. QALY, quality-adjusted life-year.

Table 2 – Outcomes, costs, effectiveness, and cost-effectiveness of providing the 21-gene assay.

A: Outcomes, costs, effectiveness, and cost-effectiveness of providing the 21-gene assay to a population of 1000 patients

Adjuvant! Online risk groups provided with 21-gene assay	Outcomes*					Costs ($ million)†		
	Provided 21-gene assay	Provided adjuvant chemo	Hospital visit for toxicity	10-y dist. rec.	10-y death	Providing 21-gene assay	Providing adjuvant chemo	Incurred prior to dist. rec.
None	0	510	87	90	74	0.00	2.37	6.27
High only	283	507	86	72	59	1.23	2.23	6.40
Intermediate only	187	497	84	79	65	0.81	2.41	6.35
Intermediate and high	470	493	84	61	50	2.04	2.27	6.48
Low only	530	371	63	85	70	2.30	2.32	6.37
Low and high	813	368	62	67	55	3.52	2.18	6.49
Low and intermediate	717	358	61	74	62	3.11	2.37	6.45
All	1000	354	60	57	46	4.33	2.23	6.58

B: Incremental outcomes, costs, effectiveness, and cost-effectiveness of providing the 21-gene assay to 1000 patients in each Adjuvant! Online risk group, compared with not providing the 21-gene assay to 1000 patients in the respective Adjuvant! Online risk group

Adjuvant! Online risk group provided with 21-gene assay	Incremental outcomes‖					Incremental costs ($ million)¶		
	Provided 21-gene assay	Provided adjuvant chemo	Hospital visit for toxicity	10- y dist. rec.	10-y death	Providing 21-gene assay	Providing adjuvant chemo	Incurred prior to dist. rec.
Low	1000	−262	−45	−9	−7	4.33	−0.08	0.18
Intermediate	1000	−71	−12	−56	−47	4.33	0.24	0.44
High	1000	−2	−2	−64	−53	4.33	−0.49	0.45

(*Continued on next page*)

Utility weights

Utility weights were derived from the EuroQol five-dimensional questionnaire index values reported in a recent study of health-related quality-of-life weights for breast cancer [30].

Analyses conducted

We conducted two sets of analyses:

1. First, we analyzed the outcomes, costs, effectiveness, and cost-effectiveness of providing (vs. not providing) the 21-gene assay to patients in each Adjuvant! Online risk group.
2. Next, we analyzed the outcomes, costs, effectiveness, and cost-effectiveness of providing (vs. not providing) adjuvant chemotherapy to patients in each of the 12 risk categories.

In each case, parameter uncertainty was accounted for by conducting probabilistic analysis across 10,000 Monte Carlo simulations.

Results

Providing the 21-Gene Assay

The results of the first analysis are summarized in Figure 2 and Table 2.

The 21-gene assay is most cost-effective for Adjuvant! Online high-risk patients, with an incremental cost-effectiveness ratio (ICER) of $1,111 per quality-adjusted life-year (QALY), followed by Adjuvant! Online intermediate-risk patients ($2,526 per QALY) and Adjuvant! Online low-risk patients ($22,440 per QALY).

At a typical willingness-to-pay threshold of $50,000 per QALY, the most cost-effective strategy is to provide the 21-gene assay to all Adjuvant! Online risk groups. Accounting for parameter uncertainty, there is a 77.94% likelihood that the 21-gene assay is cost-effective for all Adjuvant! Online risk groups and a 99.22% likelihood that it is cost-effective for at least the intermediate and high Adjuvant! Online risk groups.

Our model projects that providing the 21-gene assay to a population of 1000 patients would have an upfront cost of $4.33 million. It would reduce the number of patients receiving adjuvant chemotherapy by 156, while 27 fewer would be hospitalized because of toxicity. The costs associated with chemotherapy and hospitalization due to toxicity would fall by $0.14 million. Over 10 years, 33 fewer patients would experience a distant recurrence and 28 fewer would die of breast cancer. The costs of treatment following distant recurrence and end-of-life care would fall by $1.82 million, but the costs of following up distant recurrence-free patients would increase by $0.31 million, largely because of patients living longer in the distant recurrence-free state. Total lifetime costs would increase by $2.46 million.

Providing Adjuvant Chemotherapy

The results of the second analysis are summarized in Table 3.

For 21-gene assay low-risk patients, providing adjuvant chemotherapy increases costs yet results in worse outcomes. Conversely, for 21-gene assay high-risk patients, adjuvant chemotherapy improves outcomes and reduces costs.

Table 2 – *continued*

			Effectiveness[‡]		Cost-effectiveness of 21-gene assay[§]			
Incurred following dist. rec.	Incurred over last 3 mo of life	Total lifetime costs	Life-years	QALYs	ICER	Prob. CE ($20k) (%)	Prob. CE ($50k) (%)	Prob. CE ($100k) (%)
2.64	2.58	13.86	14,311	11,063	N/A	0.06	0.00	0.00
2.17	2.12	14.09	14,580	11,276	$1,111	0.96	0.19	0.08
2.35	2.30	14.19	14,475	11,193	D	0.22	0.07	0.05
1.89	1.84	14.42	14,745	11,407	$2,526	58.51	21.28	11.14
2.47	2.41	15.75	14,407	11,147	D	0.03	0.00	0.00
2.00	1.96	15.99	14,677	11,361	D	0.68	0.41	0.30
2.18	2.13	16.08	14,571	11,278	D	0.14	0.11	0.11
1.72	1.68	16.32	14,841	11,492	$22,440	39.40	77.94	88.32

			Incremental effectiveness[#]		Cost-effectiveness of 21-gene assay[**]			
Incurred following dist. rec.	Incurred over last 3 mo of life	Total lifetime costs	Life-years	QALYs	ICER ($)	Prob. CE ($20k) (%)	Prob. CE ($50k) (%)	Prob. CE ($100k) (%)
−0.32	−0.31	3.58	181	160	22,440	40.25	78.46	88.73
−1.53	−1.50	1.77	877	699	2,526	98.27	99.40	99.62
−1.64	−1.61	0.84	953	755	1,111	99.55	99.82	99.84

CE, cost-effectiveness; chemo, chemotherapy; dist., distant; ICER, incremental cost-effectiveness ratio; Prob., probability; QALY, quality-adjusted life-year; rec., recurrence.

* Number of events per 1000 patients.

† Costs per 1000 patients (2012 Canadian dollars). Costs for "providing adjuvant chemotherapy" include costs of treating any resulting toxicity. Costs "incurred following distant recurrence" exclude costs incurred during last 3 mo of life.

‡ Life-years and QALYs per 1000 patients.

§ ICER, ICER for the strategy in question versus the next-less-expensive nondominated strategy. Where ICER is not provided: "D" = strategy is dominated (more costly and less effective than at least one other strategy). Final three columns report the probability that the strategy in question is the most cost-effective at a willingness-to-pay value of $20,000, $50,000, or $100,000, respectively, for a QALY.

‖ *Additional* events per 1000 patients compared with not providing 21-gene assay.

¶ *Additional* costs per 1000 patients compared with not providing 21-gene assay (2012 Canadian dollars).

Additional life-years and QALYs per 1000 patients compared with not providing 21-gene assay.

** ICER, ICER for providing versus not providing the 21-gene assay to patients in the respective Adjuvant! Online risk group. Final three columns report the probability that the 21-gene assay is cost-effective for that Adjuvant! Online risk group at a willingness-to-pay value of $20,000, $50,000, or $100,000, respectively, for a QALY.

Accounting for parameter uncertainty, the likelihood that adjuvant chemotherapy is cost-effective is less than 39% for 21-gene assay low-risk patients but is more than 98% for 21-gene assay high-risk patients.

For 21-gene assay intermediate-risk patients, the cost-effectiveness of adjuvant chemotherapy is conditional upon Adjuvant! Online risk. For patients at low Adjuvant! Online risk and intermediate 21-gene assay risk, chemotherapy has an ICER of $44,088 per QALY. Although this ICER is below a typical willingness-to-pay threshold of $50,000 per QALY, the probability that chemotherapy is cost-effective at this willingness-to-pay threshold is just 50.59%. The cost-effectiveness of chemotherapy is therefore highly uncertain for patients at low Adjuvant! Online risk and intermediate 21-gene assay risk. For patients at intermediate or high Adjuvant! Online risk and intermediate 21-gene assay risk, chemotherapy is likely to be cost-effective, with an ICER of $1,776 per QALY (probability cost-effective 77.65%) or $1,778 per QALY (82.31%) respectively.

Conclusions

The 21-gene assay appears to be cost-effective for Ontario patients with lymph node–negative, estrogen receptor– and/or progesterone receptor–positive, HER2/neu-negative early breast cancer. It is most cost-effective for patients considered to be at intermediate or high risk using Adjuvant! Online.

In the opinion of the expert panel convened by the Ontario Ministry of Health and Long-Term Care, the results of Adjuvant! Online can often be approximated by clinician judgment. It follows that in cases in which Adjuvant! Online is not used as an initial risk stratification tool, the 21-gene assay is most

Table 3 – Outcomes, costs, effectiveness, and cost-effectiveness of providing adjuvant chemotherapy.

Adjuvant! Online risk group	21-gene assay risk group (if provided)	Adjuvant chemotherapy (if provided)	Outcomes*		Costs ($ million)†			
			10- y dist. rec.	10-y death	Providing 21-gene assay	Providing adjuvant chemo	Incurred prior to dist. rec.	Incurred following dist. rec.
Low	Low	None	25	21	4.33	0.00	6.94	0.81
		CMF	35	29	4.33	2.54	6.49	1.13
	Intermediate	None	57	47	4.33	0.00	6.70	1.75
		TC	41	33	4.33	5.20	6.45	1.31
	High	None	243	203	4.33	0.00	5.39	6.54
		FEC-D	60	49	4.33	7.43	6.30	1.87
	None	None	66	54	0.00	0.00	6.62	2.04
		CMF	45	37	0.00	2.54	6.41	1.45
Intermediate	Low	None	42	34	4.33	0.00	6.82	1.30
		CMF	43	35	4.33	2.54	6.44	1.36
	Intermediate	None	131	108	4.33	0.00	6.16	3.77
		TC	57	47	4.33	5.20	6.33	1.78
	High	None	448	382	4.33	0.00	4.18	10.55
		FEC-D	67	55	4.33	7.43	6.24	2.10
	None	None	202	168	0.00	0.00	5.65	5.64
		TC	56	45	0.00	5.20	6.33	1.76
High	Low	None	41	34	4.33	0.00	6.82	1.29
		CMF	43	35	4.33	2.54	6.43	1.36
	Intermediate	None	131	108	4.33	0.00	6.15	3.80
		TC	58	47	4.33	5.20	6.32	1.80
	High	None	448	381	4.33	0.00	4.17	10.58
		FEC-D	69	56	4.33	7.43	6.23	2.14
	None	None	239	199	0.00	0.00	5.40	6.51
		FEC-D	51	42	0.00	7.43	6.37	1.63

(*Continued on next page*)

cost-effective for patients judged to be at above average risk of distant recurrence.

Adjuvant chemotherapy appears cost-effective for 21-gene assay high-risk patients, but not for low-risk patients. For patients at intermediate 21-gene assay risk, adjuvant chemotherapy appears cost-effective for those considered to be at intermediate or high risk using Adjuvant! Online. For 21-gene assay intermediate-risk patients who otherwise appear to be at low risk of distant recurrence, the cost-effectiveness of adjuvant chemotherapy is uncertain.

Our findings are consistent with those of existing cost-effectiveness analyses of the 21-gene assay [16,39–44]. With the exception of the recent analysis by Reed et al. [44], however, these previous analyses share a number of limitations: none considers provision of the 21-gene assay conditional upon Adjuvant! Online risk; most conflate the intermediate and high 21-gene assay risk groups; and all implicitly assume that the 21-gene assay replaces, rather than complements, Adjuvant! Online or clinician judgment in adjuvant chemotherapy decision making. The Reed et al. analysis addresses these limitations but has a number of limitations of its own. In particular, it makes flawed assumptions in its interpretation of the data from Lo et al. that inform the proportion of patients assumed to receive chemotherapy: first, that a recommendation to provide hormonal therapy in the absence of the 21-gene assay results necessarily implies that the patient is low risk; and second, that a clinician's recommendation of "equipoise" instead represents a recommendation to provide chemotherapy. The Reed et al. analysis also makes the assumption that in the absence of the 21-gene assay results, no low-risk patients would receive chemotherapy but every intermediate- or high-risk patient would receive chemotherapy (this assumption in particular serves to exaggerate the benefit of the 21-gene assay). Critically, no existing analyses, including the Reed et al. analysis, directly evaluate the cost-effectiveness of adjuvant chemotherapy for patients in specific risk categories. Our analysis comprehensively addresses all these limitations.

Nevertheless, our analysis also has limitations. Most notably, the allocation of patients among risk categories and the estimates of the baseline risk of distant recurrence were derived from unpublished retrospective data, while the relative risk estimates were derived by using retrospective data and the results of trials that may not be directly comparable. Our model also did not consider local recurrence or the possibility of minor or long-term adverse events resulting from chemotherapy, while the impact of the 21-gene assay on clinician decision making was derived from a small study conducted outside the Ontario context. Finally, our analysis does not control for the potential confounding effects of HER2/neu positivity across the key validation studies [6,7]. With the introduction of trastuzumab, HER2/neu-positive patients currently undertake a treatment pathway that is distinct from that taken by HER2/neu-negative patients, and so these patients are generally not candidates for the 21-gene assay. It is unclear what effect removing HER2/neu-positive patients would have on the prognostic and predictive value of the 21-gene assay [6].

Our findings will be of considerable interest to policymakers and health care providers. In the United States, the cost of the 21-gene assay is currently covered by Medicare and some major insurance companies [45]. In the United Kingdom, the National Institute for Health and Care Excellence (formerly the National

Table 3 – *continued*

		Effectiveness[‡]		Cost-effectiveness of adjuvant chemotherapy[§]			
Incurred during last 3 mo of life	Total lifetime costs ($ million)	Life-years	QALYs	ICER	Prob. CE ($20k) (%)	Prob. CE ($50k) (%)	Prob. CE ($100k) (%)
0.79	12.67	15,365	11,930	D	11.28	15.43	17.34
1.10	15.39	15,140	11,691				
1.71	14.28	14,846	11,519	$44,088	40.96	50.59	54.41
1.28	18.37	15,039	11,611				
6.40	22.45	12,067	9,317	CE	98.99	99.41	99.54
1.83	21.56	14,732	11,368				
1.99	10.65	14,689	11,394	$7,389	63.22	68.65	70.73
1.42	11.82	14,965	11,552				
1.27	13.51	15,095	11,716	D	34.12	37.52	38.85
1.32	15.78	15,015	11,592				
3.69	17.74	13,696	10,607	$1,776	73.79	77.65	78.85
1.73	19.16	14,781	11,407				
10.34	29.20	9,506	7,293	CE	99.99	100.00	100.00
2.05	21.94	14,608	11,269				
5.51	16.80	12,622	9,757	CE	99.79	99.87	99.89
1.72	15.01	14,794	11,417				
1.26	13.49	15,100	11,720	D	32.66	36.19	37.58
1.33	15.80	15,010	11,588				
3.71	17.79	13,685	10,599	$1,778	78.74	82.31	83.91
1.76	19.21	14,769	11,397				
10.37	29.25	9,494	7,283	CE	100.00	100.00	100.00
2.09	22.02	14,586	11,252				
6.37	18.28	12,097	9,341	CE	100.00	100.00	100.00
1.59	17.02	14,865	11,474				

CE, cost-effectiveness; chemo, chemotherapy; CMF, oral cyclophosphamide 100 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2, given 4-weekly for six cycles; dist., distant; FEC-D, 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2, given 3-weekly for three cycles, followed by docetaxel 100 mg/m^2 given 3-weekly for three cycles; ICER, incremental cost-effectiveness ratio; Prob., probability; QALY, quality-adjusted life-year; rec., recurrence; TC, docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2, given 3-weekly for four cycles.

* Number of events per 1000 patients.

† Costs per 1000 patients (2012 Canadian dollars). Costs for "providing adjuvant chemotherapy" include costs of treating any resulting toxicity. Costs "incurred following distant recurrence" exclude costs incurred during last 3 mo of life.

‡ Life-years and QALYs per 1000 patients.

§ ICER, ICER for providing (vs. not providing) adjuvant chemotherapy. Where ICER is not provided: "D" = adjuvant chemotherapy is dominated (more costly and less effective); "CE" = adjuvant chemotherapy is less costly and more effective. Final three columns report the probability that adjuvant chemotherapy is cost-effective at a willingness-to-pay for a QALY of $20,000, $50,000, or $100,000, respectively.

Institute for Health and Clinical Excellence) recently issued preliminary guidance that recommended funding the 21-gene assay through the National Health Service (NHS) only in cases where a patient is initially assessed as being at "intermediate risk," where the decision to provide chemotherapy remains "unclear," and where the 21-gene assay is provided by the manufacturer to the NHS at the price offered through a "confidential arrangement agreed with NICE" [46]. In Ontario, based in part on our findings, the Ontario Health Technology Advisory Committee has proposed that the 21-gene assay be funded for patients as part of a field evaluation, with the aim of evaluating "further correlations between [the 21-gene assay] and Adjuvant! Online and other clinical variables, as well as the clinical impact of [the 21-gene assay] on patient and practitioner decision-making" [47].

Our findings will also be of interest to clinicians faced with a climate of constrained resources and the difficult decision of whether to provide chemotherapy, particularly to patients in the intermediate 21-gene assay risk group. This clinical uncertainty is the primary motivation behind the ongoing TAILORx trial [11,12].

While the 21-gene assay is the first genomic-based breast cancer decision aid to be evaluated by the Ontario Ministry of Health and Long-Term Care, and remains the only genomic-based breast cancer decision aid used in clinical practice in Ontario, a number of alternative decision aids have recently become available [48–50]. Our modeling framework may be adapted to evaluate the clinical- and cost-effectiveness of these and future genomic-based breast cancer decision aids, and potentially guide adjuvant chemotherapy decisions on the basis of multiple genomic- and non–genomic-based decision aids used in conjunction. In the meantime, our analysis provides policymakers and clinicians with guidance, based on the best evidence currently available, on the clinical- and cost-effective provision of the 21-gene assay and adjuvant chemotherapy.

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